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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/589,290	08/11/2006	Susan Wimer-Mackin	LIGO-009/02US	5685

58249 7590 05/12/2009

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EXAMINER	
DUFFY, PATRICIA ANN	

ART UNIT	PAPER NUMBER
1645	

MAIL DATE	DELIVERY MODE
05/12/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/589,290	WIMER-MACKIN, SUSAN	
	Examiner	Art Unit	
	Patricia A. Duffy	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 February 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *49-77* is/are pending in the application.

4a) Of the above claim(s) *68-77* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *49-67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/06; 12/06; 4/07; 9/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The response filed 2-12-09 has been entered into the record.

Priority

Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, the provisional application upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 48-67 of this application. In the instant case neither of the provisional filings provides for written description and conception of compositions comprising mucosal administration devices, dry powder formulations, specific adjuvants such as signaling transducer receptor of LPS, other positively charged polysaccharides, toll-like receptors in the now claimed combinations.

Drawings

The drawings in this application have been accepted. No further action by Applicant is required.

Specification

The disclosure is objected to because of the following informalities: Tables 2 and 5 cannot be read as the numbers have been cut-off.

Appropriate correction is required.

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Information Disclosure Statement

The information disclosure statements have been considered. Initialed copies are enclosed.

Election/Restrictions

Applicant's election with traverse of Group I in the response filed 2-12-09 is acknowledged. The traversal is on the ground(s) that Applicants request rejoinder under of process claims that depend from or otherwise require all the limitations of allowable product claims. This is not found persuasive at this point in prosecution because until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained.

The requirement is still deemed proper and is therefore made FINAL.

Claims 68-77 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the response filed 2-12-09.

Claim Objections

Claims 64-67 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The claims recite characteristics of an immune response. The characteristics of the immune response are not seen to properly further limit the composition per se. For example, the term "primary immune response" is an art term indicating that the immune response is generated in a naive animal not having seen the antigen before. This does not limit the structure of the composition per se, but is directed to the property of the animal to which the composition

is administered. Therefore, these properties do not structurally limit the composition per se as they are characteristics of the animal's immune response.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 49-67 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

As to claims 49-67, the specification defines anthrax peptide at paragraphs [046]-[049] of the specification and includes homolgous variants and fragments and of any the full length native protective antigen (PA), lethal factor (LF), edema factor (EF), poly (gamma-D-glutamic acid (PGA) and BclA. The specification includes in the definition epitopes and immunogenic fragments. The specification teaches how to make variants and describes that which is defined in the art as "epitopes" but does not describe any functional variant or functional immunogenic epitopes. The written description of the specification does not provide written description of functional variants and functional immunogenic/epitopes fragments of any of the above native anthrax antigens described by the art. The courts have held that when the specification discloses at most a specific sequence known to the inventor which encodes a single protein having a specific structure

and biological characteristics, the disclosure is not commensurate with the claims (*Ex parte Maizel*, 27 USPQ2d 1662). Other than identifying native full length anthrax antigens, the specification does not teach those single residues in amino acid residues within that can be inserted, substituted or deleted, to arrive at a mutation that maintains functionally of the anthrax peptide set forth in the claims. Although the disclosure would put the skilled artisan in possession of multiple different individual single substitutions, insertions or deletions that may or may not retain activity, the level of skill and knowledge in the art is such that one of ordinary skill would not be able to identify without further testing, which of those variants would have the claimed activities of ameloriation or prevention of at least one symptom of anthrax disease. The use of antibody levels were admitted by applicants in several instances in the specification as not to correlate with prevention of disease. See for example paragraph [0113] that states "It is well known in the literature that protection from anthrax does not always correlate with titer.". Applicants own data support this finding in the literature. The specification does not describe any variant of a natural/native anthrax peptide that has the requisite claimed functional activity. A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1405 (Fed. Cir. 1997 (bracketed material in original). The teachings of the specification do not describe any immunogenic fragments or epitopes that provides for an immune response that can ameliorate or prevent at least one symptom of anthrax disease. While the specification defines epitopes and describes linear and conformational epitopes consistent with the definition in the art, it fails to teach linear or conformational epitopes of any of the anthrax peptide antigens of the art that function as claimed, so that the skilled artisan could immediately envision, or recognize at least a substantial number of members of the claimed genus. Moreover, the specification fails to disclose which

chemical structures are essential to the function of any fragment/epitope so that the functional activity of the fragment/epitope could be ascertained/maintained. Thus, the specification fails to adequately describe at least a substantial number of members of the genus of fragments/epitopes and corresponding to either the native/natural anthrax peptide(s) or any variant thereof encompassed by the claims. As evidenced by Greenspan et al. (Nature Biotechnology 7: 936-937, 1999), defining epitopes is not as easy as it seems. Greenspan et al. recommends defining an epitope by the structural characterization of the molecular interface between the antigen and the antibody is necessary to define an "epitope" (page 937, column 2). According to Greenspan et al., an epitope will include residues that make contact with a ligand but are energetically neutral, or even destabilizing to binding. Furthermore, an epitope will not include any residue not contacted by the antibody, even though substitution of such a residue might profoundly affect binding. Accordingly, it follows that the immunoepitopes (of an antigen) that can elicit an antibody response to a given pathogen can only be identified empirically. While the art can conventionally scan for ***potential*** contiguous antibody epitopes using conventional art accepted algorithms (Greenbaum et al, Journal of Molecular Recognition, 20(2):75-82, 2007), these methods do not identify discontinuous epitopes which are identified by crystallization of antibody/antigen complexes. The quality of the methods for B cell epitope prediction was widely considered to be too poor to be employed as a reliable tool by immunologists (paragraph spanning pages 75-82). Furthermore, these methods also do not identify those microbial that have cross-reactivity with an apoptotic cell epitope. The art recognizes that defining epitopes is not easy and there is a confusing divergence between the textbook definition of epitope and the definition that is in use in published descriptions of experimental investigations (Greenspan et al, Nature Biotechnology 17:936-937, 1999). Even as late as 2005 the art recognized that single-scale amino acid propensity profiles could not be used to predict epitope location reliably (Blythe et al, Protein Science 14:246-248, 2005). Therefore, even with art tools, it would be

unpredictable to use those tools to attempt to identify regions that were important for eliciting an immune response as claimed.

As to claims 60-63, the claims are drawn to dry powder formulation for mucosal administration in combination with one or more devices for administering one or more doses. The teachings of the specification are limited to the teaching at page [0147] that indicated the "Dry powder vaccines were formulated by West Pharmaceutical Services and loaded in to Valois Monopowder single-use nasal administration devices". The specification does not disclose any dry powder formulation and the specification does not teach how to make dry powder vaccines in a mucosal administration device. The specification does not teach how to make the dry powder formulations used in the specification. In the instant case, Applicants claim a dry powder vaccine, the specification teaches that the mode of administration, dose of protective antigen and particular adjuvant or combinations of adjuvants materially affect the performance of the immunogen. Applicants are claiming in broad terms a dry powder mucosal vaccine but do not teach how to make such or do not reference any particular means in the art to arrive at such. In fact, Applicants turned to a Pharmaceutical Service, who processed the combinations by unknown means containing perhaps unknown carriers, emulsifiers or agents to arrive at an unknown not reproducible dry powder composition that was administered intranasally to rabbits. Therefore, Applciants have not conveyed by means of written description that Applicants were in possession of the genus of formulation of dry powder vaccines as claimed.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116.). Applicants are directed to Revision I of

the Written Description Training materials, posed 4/11/08: <http://www.uspto.gov/web/menu/written.pdf> and MPEP 2163. As such, the skilled artisan would not readily appreciate from the comparison that Applicants were in possession of the now claimed invention. The courts have held that possession of a genus may not be shown by merely describing how to obtain members of the claimed genus (i.e. make and test to see if they lack the requisite activity) or how to identify their common structural features. See *University of Rochester*, 358 F.3d at 927, 69 USPQ2d at 1895 and *Ex Parte Kubin et al*, Appeal 2007-0819, May 31, 2007. In addition, the court has held that a method of identification of compounds (i.e. screening for variants) is not a description of the compounds *per se* that meet the requisite function to use in the associated methods. *University of Rochester v. G.D. Searle & Co.* 69 USPQ2D 1886 (CAFC 2004. Finally, function does not describe a structure, because the specification does not provide relevant identifying characteristics , including functional characteristics when coupled with known or disclosed correlation between function and structure. The courts have held that in these instances, the specification lacks written description see *Enzo Biochem Inc. v. Gen-Probe Inc.* 63 USPQ2D 1609 (CAFC 2002) and *University of Rochester v. G.D. Searle & Co.* 69 USPQ2D 1886 (CAFC 2004). When the genus is large and the specification lacks a known (art described) or disclosed correlation between structure and function, the written description of the specification does not convey possession of the claimed genus.

Based on the lack of knowledge and predictability in this art, the lack of corresponding homologs and lack of any characterized sequenced protein homologs, lack of any characterized immunogenic fragment/epitope those of ordinary skill in the art would not conclude that the Applicant was in possession of the claimed genus of anthrax peptide variants or in possession of immunogenic fragments or epitopes that functioned to ameliorate or prevent at least one symptom of anthrax disease as claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 49-53, 57, 58 and 60-67 rejected under 35 U.S.C. 102(a) as being anticipated by Miksztra et al (JID, 191:278-288, January 15, 2005 record on 1449).

Miksztra et al teach a dry powder formulation of rPA, /CpG/trehalose/chitosan powder and loaded into capsules. The capsules were loaded into a intranasal delivery device (see Figure 1C) on page 281. Miksztra et al therefore anticipate the instantly claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 49-57 and 60-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schneerson et al (2006/0134143 published June 22, 2006 with priority to 60/476,598 filed on June 3, 2003).

Schneerson et al teach recombinant PA conjugated to a PGA peptide intended for immunization against anthrax paragraphs [0010-0011] and [0094] of the specification. Schneerson et al teach that the gamma PGA conjugate can be administered to subjects by a variety of mucosal administration routes including oral, rectal, intranasal or intrapulmonary at paragraph [0126]. Schneerson et al teach that the composition includes adjuvants such as MPL among many other suitable adjuvants well known in the art can be included in the compositions at paragraph [0127]. Schneerson et al teach that the conjugate can be dispersed in a base or vehicle and the vehicle can be provided in a variety of forms including fluid, gels, pastes, powders, microspheres and films for direct application to a mucosal surface at paragraph [0128]. Schneerson et al teach that the composition includes kits, packages and multi-container units containing the pharmaceutical compositions optionally multi-dose formulations for use in the prevention or treatment of anthrax. Schneerson et al teach that optional dispensing means can be provides for example, a pulmonary or intranasal spray applicator.

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to add the recombinant PA conjugated to a PGA peptide to the MPL adjuvant and formulate the immunogenic composition as a dry powder for use a dispensing means for intranasal or intrapulmonary administration in single or mulitdose formulations according to Schneerson et al because Schneerson et al teach that the recombinant PA conjugated to a PGA peptide can be so formulated and dispensed to the mucosal sites such as pulmonary, oral or nasal. The dose, unit or multi-unit formulation packaging along with single or multi-use devices are design choices well established in the art and the choice of unit dosing and multi or single use despensing devices are well within the skill of the pharmaceutical arts.

Claim 49-58 and 64-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schneerson et al (2006/0134143 published June 22, 2006 with priority to 60/476,598 filed on June 3, 2003) in view of Sigma Chemical Catalog 2002-2003, page 86, MPL+TDM emulsion.

Schneerson et al teach recombinant PA conjugated to a PGA peptide intended for immunization against anthrax paragraphs [0010-0011] and [0094] of the specification. Schneerson et al teach that the gamma PGA conjugate can be administered to subjects by a variety of mucosal administration routes including oral, rectal, intranasal or intrapulmonary at paragraph [0126]. Schneerson et al teach that the composition includes adjuvants such as MPL among many other suitable adjuvants well known in the art can be included in the compositions at paragraph [0127]. Schneerson et al teach that the conjugate can be dispersed in a base or vehicle and the vehicle can be provided in a variety of forms including fluid, gels, pastes, powders, microspheres and films for direct application to a mucosal surface at paragraph [0128]. Schneerson et al teach that the composition includes kits, packages and multi-container units containing the pharmaceutical compositions optionally multi-dose formulations for use in the prevention or treatment of anthrax. Schneerson et al teach that optional dispensing means can be provides for example, a pulmonary or intranasal spray applicator. Schneerson et al differ by not teaching combination of two adjuvants with the recombinant PA for mucosal administration in a device.

Sigma Chemical Catalog teaches that MPL and TDM emulsion have been prepared in a manner to reduce the undesirable side effects of toxicity and allerginicity but still provide potent stimulus to the immune system.

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the recombinant PA conjugated to a PGA peptide to the MPL and TDM adjuvant of Sigma Chemical Catalog and formulate the immunogenic

composition as a fluid, gel, paste, powder, microsphere or film and place in a single or multi dose dispensing device such as an inhaler or syringe or dropper bottle for mucosal delivery of the composition because Schneerson et al teach that the recombinant PA conjugated to PGA can be formulated with suitable adjuvants and dispersed in a vehicle or base that provides for direct application at a mucosal surface. The dose, unit or multi-unit formulation packaging along with single or multi-use devices are packaging design choices well established in the art and the choice of unit dosing and multi or single use dispensing devices are well within the skill of the pharmaceutical arts.

Claim 49-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schneerson et al (2006/0134143 published June 22, 2006 with priority to 60/476,598 filed on June 3, 2003) in view of Alpar et al , In:MVADS Conference 4th-6ht of June 2003, Dublin, Republic of Ireland.

Schneerson et al teach recombinant PA conjugated to a PGA peptide intended for immunization against anthrax paragraphs [0010-0011] and [0094] of the specification. Schneerson et al teach that the gamma PGA conjugate can be administered to subjects by a variety of mucosal administration routes including oral, rectal, intranasal or intrapulmonary at paragraph [0126]. Schneerson et al teach that the composition includes adjuvants such as MPL among many other suitable adjuvants well known in the art can be included in the compositions at paragraph [0127]. Schneerson et al teach that the conjugate can be dispersed in a base or vehicle and the vehicle can be provided in a variety of forms including fluid, gels, pastes, powders, microspheres and films for direct application to a mucosal surface at paragraph [0128]. Schneerson et al teach that the composition includes kits, packages and multi-container units containing the pharmaceutical compositions optionally multi-dose formulations for use in the prevention or treatment of anthrax. Schneerson et al teach that optional dispensing means can be provides for example, a pulmonary or intranasal spray applicator. Schneerson et al differ by not

teaching combination of two adjuvants (MPL and Chiotosan) with the recombinant PA for mucosal administration in a device.

Alpar et al teach that successful mucosal vaccination is dependent on the development of effective mucosal adjuvants. Alpar et al teach that the adjuvants that have been shown to be mucosally effective ro monophosphoryl lipid A (MPL), toxins and immunostimulatory DNA sequences (i.e. the instant agnosits of toll-like receptors) (see paragraph 1). Alpar et al also teach that in previous studies they have shown that chitosan is able to enhance the effects of other adjuvants when administered intranasally.

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to add the recombinant PA conjugated to a PGA peptide to the mucosal adjuvant MPL and the chitosan adjuvant of Alpar et al and formulate the immunogenic composition as a dry powder for use a dispensing means for intranasal administration in single or mulitdose formulations according to Schneerson et al because Schneerson et al teach that the recombinant PA conjugated to a PGA peptide can be so formulated with the MPL and other mucosal adjuvants and dispensed to the mucosal sites such as nasal and Alpar et al teach that chitosan is able to enhance the effects of other adjuvants when administered mucosally to the nose (i.e. intranasal). The dosage, unit or multi-unit formulation packaging along with single or multi-use devices are design choices well established in the art and the choice of unit dosing and multi or single use dispensing devices are well within the skill of the pharmaceutical arts.

Status of the Claims

Claims 49-67 stand rejected. Claims 68-77 are withdrawn from consideration.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy whose telephone number is 571-272-0855. The examiner can normally be reached on M-Th 6:30 am - 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisor Robert Mondesi can be reached at 571-272-0956.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Patricia A. Duffy/
Primary Examiner